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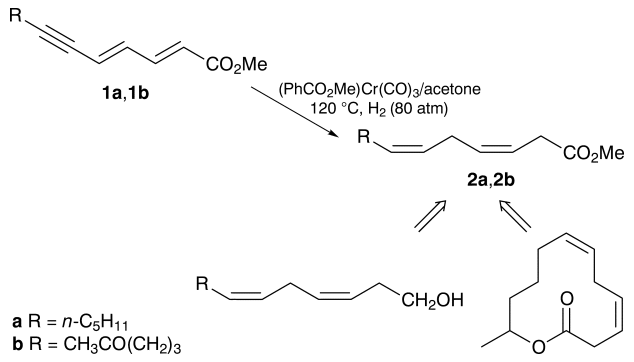
Access to 2,4-Dien-6-ynoic Acid Esters Using Selenium Chemistry. Formal Synthesis of *Z,Z*-Dodeca-3,6-dien-1-ol (Trail Pheromone Mimic of the Subterranian Termite *Reticulitermes virginicus*) and *Z,Z*-Dodeca-3,6-dien-11-olide (Aggregation Pheromone of the Grain Beetles *Oryzaephilus mercartor* and *O. surinamensis*)†

Andrei A. Vasil'ev,[a] Lars Engman[b] and Edward. P. Serebryakov*[a]

[a]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russia*
[b]*Institute of Chemistry, Department of Organic Chemistry, Uppsala University, Box 531, 751 21 Uppsala, Sweden*

Esters of 2,4-dien-6-ynoic acids were prepared from terminal acetylenes by lithiation, 1,2-addition to acrolein, orthoester Claisen–Johnson rearrangement and α-(4-methoxyphenyl)selenation/oxidative elimination to introduce the α,β-unsaturation.

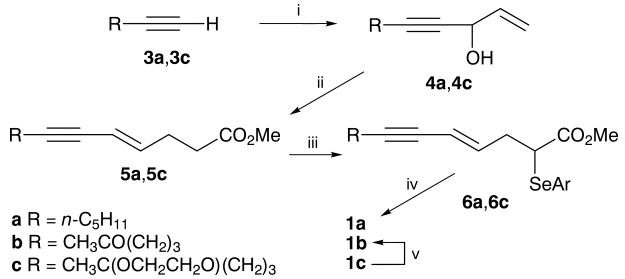
Recently, some of us showed that hydrogenation of alka-2,4-dien-6-ynoates **1a,b** (Scheme 1) over chromium carbonyl catalysts cleanly leads to the corresponding 3*Z*,6*Z*-homoconjugated dienes **2a,b**.[1–3] In view of the known capacity of (arene)$Cr(CO)_3$ complexes to catalyze hydrogenation of conjugated dienes (1,4-*cis*-addition) and alkynes (1,2-*cis*-addition),[4] the result can be rationalized assuming a higher affinity of the catalyst for the diene than for the acetylene system. With this approach, the two pheromones *Z,Z*-dodeca-3,6-dien-1-ol (trail pheromone mimic of the subterranian termite *Reticulitermes virginicus*)[5] and *Z,Z*-dodeca-3,6-dien-11-olide (aggregation pheromone of the grain beetles *Oryzaephilus mercartor* and *O. surinamensis*)[6] were successfully prepared as outlined in Scheme 1. However, the yields of dienynes **1** in the Horner–Emmons olefination of alk-2-ynals used for their preparation never exceeded 45%.



Scheme 1

Here, we report an alternative procedure for the preparation of dienynes **1** from 4-en-6-ynoates **5**, using α-arylselenenation/oxidative elimination as a key step. Since the pioneering work by Jones and Sharpless,[7] organoselenium chemistry has been frequently used for the introduction of unsaturation into organic molecules.[8] However, relatively few reports are concerned with aliphatic esters containing additional multiple bonds,[9–11] and conjugated 2,4-dien-6-ynoates have, to the best of our knowledge, not been prepared in this way. The required methyl 4-en-6-ynoates **5** were readily prepared in a two step sequence from the corresponding terminal acetylenes **3** as shown in Scheme 2 (*cf.* ref. 12). Due to incomplete conversion of the starting material, α-selenenation using a routine protocol (lithium diisopropylamide, LDA, followed by addition of Ph_2Se_2 to the resulting carbanion[9–11]) was found to be unsuitable. Probably, α-phenylseleno ester initially formed is much more acidic than the starting material and is easily deprotonated and selenated again. The use of an excess of the base and Ph_2Se_2 did not improve the yield appreciably. Furthermore, all components exhibited similar R_f values on a TLC plate and were inseparable by column chromatography (this problem is briefly addressed in the experimental part of ref. 9). A better result was obtained by cannulating a solution of the carbanion into the diselenide solution. By this inverse addition, the ester enolate is immediately quenched and a high conversion and selectivity towards monoselenation are achieved. To facilitate chromatographic purification, bis(4-methoxyphenyl) diselenide was used instead of the unsubstituted diphenyl diselenide. Under these conditions, pure 2-(4-methoxyphenylseleno)-4-en-6-ynoic esters **6a,c** were obtained in 51–52% yields.

Oxidative elimination of the 4-methoxyphenylseleno moiety afforded the target dienynic esters in high yields, predominantly as the *E,E*-isomers. Previously, this substituent was found to undergo oxidative elimination more readily than the phenylseleno group.[13]



Scheme 2 *Reagents and conditions*: i, Bu^{n}Li, THF, then acrolein; ii, $MeC(OMe)_3$, $EtCO_2H$, 115 °C, 6 h (**3a** to **5a**, 52%; **3c** to **5c**, 71%); iii, LDA, then Ar_2Se_2 (Ar = 4-methoxyphenyl) (**5a** to **6a**, 51%; **5c** to **6c**, 52%); iv, H_2O_2, THF, room temp., 3 h (**6a** to **1a**, 73%); v, $(HO_2C)_2$, acetone/H_2O (4:1), reflux, 3 h (**6c** to **1b**, 93%)

*To receive any correspondence.
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Although the yields in the selenenation step are still only moderate,[8] we believe that our methodological findings will prove useful for the preparation of related polyunsaturated natural products.

Experimental

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 spectrometer operating at 299.903 MHz (^{1}H NMR) and 75.419 MHz (^{13}C NMR). Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany. Bis(4-methoxyphenyl) diselenide[13] and 6,6-ethylenedioxyhept-1-yne **3c**[3,14,15] were prepared in anology with the literature procedure.

Methyl dodec-4-*en*-6-*ynoate* **5a**. To a stirred solution of hept-1-yne (3.2 g, 32.5 mmol) in tetrahydrofuran (THF) (20 ml) under nitrogen at −78 °C, Bu^{n}Li (13.22 ml 2.08 M solution in hexanes, 27.5 mmol) was added and the mixture was allowed to warm to room temperature during 30 min. Acrolein (1.4 g, 25 mmol) in THF (7 ml) was then added slowly at 0 °C and the mixture was stirred for 1 h. Treatment with aqueous NH_4Cl, extraction with diethyl ether, drying over Na_2SO_4 and evaporation afforded almost pure dec-1-en-4-yn-3-ol **4a**. Without purification, this material was dissolved in trimethyl orthoacetate (25 ml) and toluene (50 ml) containing propionic acid (0.1 ml) and was heated at 120 °C for 5 h while a fraction with bp 50–60 °C was collected. The residue was then stirred with water (100 ml) containing HOAc (0.6 ml) at room temperature for 30 min. Solid $NaHCO_3$ (0.5 g) was added, the organic layer was separated, the aqueous phase was extracted with diethyl ether and the combined extracts were dried and concentrated *in vacuo*. Column chromatography (pentane, then 2.5% EtOAc in pentane) afforded 2.726 g (52%) of the title compound as a colourless oil. δ_H 0.90 (t, 3H), 1.35 (m, 4H), 1.52 (m, 2H), 2.27 (t, d, *J* 7.1, 2.3, 2H), 2.40 (m, 4H), 3.68 (s, 3H), 5.51 (dm, *J* 15.8, 1H), 5.02 (dm, *J* 15.8, 1H).

Methyl 11,11-*ethylenedioxydodec*-4-*en*-6-*ynoate* **5c**. Compound **5c** was prepared as described above from 6,6-ethylenedioxyhept-1-yne **3c** (2.335 g, 15.1 mmol). Final column chromatography (5% diethyl ether in pentane, then 20% diethyl ether in pentane) afforded 2.86 g (71%) of the title compound as an 85:15 mixture of *E* and *Z* isomers. *E*-Isomer δ_H 1.32 (s, 3H), 1.63 (m, 2H), 1.74 (m, 2H), 2.31 (td, *J* 7.0, 1.9, 2H), 2.40 (m, 4H), 3.67 (s, 3H), 3.94 (m, 4H), 5.51 (dm, *J* 15.9, 1H), 6.02 (dm, *J* 15.6). Characteristic peaks of the *Z*-isomer were found at δ 2.60 (q, *J* 7.6), 3.68 (s), 5.81 (dm, *J* 10.3).

Methyl 2-(4-*methoxyphenylseleno*)*dodec*-4-*en*-6-*ynoate* **6a**. Diisopropylamine (0.327 ml, 2.5 mmol) was added to a mixture of Bu^{n}Li (0.816 ml 2.45 M solution in hexanes, 2.0 mmol) and THF (3 ml) under nitrogen at −78 °C. After 10 min, methyl dodec-4-en-6-ynoate (0.208 g, 1 mmol) in THF (1 ml) was added dropwise and stirring was continued for 30 min. The reaction mixture was then cannulated into a solution of bis(4-methoxyphenyl) diselenide (0.5 g, 1.34 mmol) in THF (3 ml) at −78 °C and stirring was continued for 30 min. HOAc (0.3 ml) was added and the mixture was allowed to warm to room temperature before work up. Column chromatography (2.5% EtOAc in pentane) afforded 0.205 g (51%) of the title compound as a colourless oil. δ_H *E*-isomer 0.89 (t, 3H), 1.34 (m, 4H), 1.51 (m, 2H), 2.27 (td, *J* 7.0, 2.1, 2H), 2.38–2.64 (m, 2H), 3.52 (dd, *J* 8.6, 6.6, 1H), 3.63 (s, 3H), 3.81 (s, 3H), 5.51 (dm, *J* 15.9, 1H), 5.96 (dt, *J* 15.9, 7.2, 1H), 6.83 (d, *J* 8.8, 2H), 7.46 (d, *J* 8.8, 2H). δ_C 13.9, 19.3, 22.2, 28.4, 31.0, 34.6, 41.7, 52.0, 55.2, 78.6, 90.4, 113.0, 114.6, 117.0, 138.2, 138.3, 160.4, 172.5.

Methyl 2-(4-*methoxyphenylseleno*)-11,11-*ethylenedioxydodec*-4-*en*-6-*ynoate* **6c**. Compound **6c** was prepared similarly from the crude methyl 11,11-ethylenedioxydodec-4-en-6-ynoate (0.266 g, 1 mmol). Final column chromatography (15–25% diethyl ether in pentane) afforded 0.235 g (52%) of the pure title compound as an 80:20 mixture of *E* and *Z* isomers. *E*-Isomer: δ_H 1.32 (s, 3H), 1.63 (m, 2H), 1.73 (m, 2H), 2.31 (td, *J* 6.9, 2.0, 2H), 2.47 (m, 1H), 2.60 (m, 1H), 3.52 (dd, *J* 8.8, 6.7, 1H), 3.64 (s, 3H), 3.81 (s, 3H), 3.93 (m, 4H), 5.50 (dm, *J* 15.8, 1H), 5.95 (dt, *J* 15.7, 7.3, 1H), 6.84 (d, *J* 8.9, 2H), 7.50 (d, *J* 8.9, 2H). δ_C 19.5, 23.2, 23.8, 34.8, 38.2, 41.7, 52.0, 55.2, 64.61, 78.9, 89.8, 109.8, 112.9, 114.6, 116.9, 138.29, 138.3, 160.4, 172.5.

Methyl dodeca-2,4-*dien*-6-*ynoate* **1a**. To a solution of methyl 2-(4-methoxyphenylseleno)dodec-4-en-6-ynoate (0.133 g, 0.34 mmol) in THF (3 ml), hydrogen peroxide (0.4 ml 30% aqueous solution) was added. After additional stirring at room temperature for 3 h, the mixture was treated with $NaHCO_3$ (aq.) and extracted with diethyl ether. The combined extracts were dried and concentrated *in vacuo* and the residue purified by column chromatography (2% EtOAc in pentane) to afford 0.051 g (73%) of the title compound as a 93:7 mixture of (2*E*,4*E*) and (2*E*,4*Z*) isomers. (2*E*,4*E*)-Isomer: δ_H 0.91 (t, 3H), 1.35 (m, 4H), 1.52 (m, 2H), 2.36 (td, *J* 7.0, 2.2, 2H), 3.75 (s, 3H), 5.91 (d, *J* 15.7, 1H), 5.97 (d, *J* 15.2, 1H), 6.58 (dd, *J* 15.3, 11.3, 1H), 7.27 (ddt, *J* 15.3, 11.4, 0.9, 1H). Characteristic ^{1}H NMR peaks of the (2*E*,4*Z*)-isomer were found at δ_H 2.40 (td, *J* 7.0, 2.2, 2H), 5.79 (dm, *J* 10.6, 1H), 6.41 (t, *J* 10.6, 1H), 7.76 (dm, *J* 14.8, 1H). ^{13}C NMR data were in good agreement with the literature.[2]

Methyl 11-*oxododeca*-2,4-*dien*-6-*ynoate* **1b**. Compound **1b** was prepared by the similar oxidation of methyl 2-(4-methoxyphenylseleno)-11,11-ethylenedioxydodec-4-en-6-ynoate (0.200 g, 0.443 mmol) with H_2O_2 in THF. The crude material was then deprotected by refluxing for 3 h in a 4:1 mixture of acetone and water (5 ml) containing oxalic acid (0.1 g). After the usual work up, column chromatography (30% diethyl ether in pentane) afforded 0.091 g (93%) of the title compound as an 81:19 mixture of (2*E*,4*E*) and (2*E*,4*Z*) isomers. (2*E*,4*E*)-Isomer, mp 62 °C (hexane). δ_H 1.82 (quint, *J* 6.8, 2H), 2.17 (s, 3H), 2.40 (td, *J* 7.0, 2.2, 2H), 2.56 (t, *J* 7.7, 2H), 3.76 (s, 3H), 5.90 (d, *J* 15.4, 1H), 5.94 (dt, *J* 15.5, 2.2, 1H), 6.57 (dd, *J* 15.9, 11.6, 1H), 7.24 (dd, *J* 15.3, 11.5, 1H). δ_C 19.1, 22.3, 30.1, 42.2, 51.7, 80.1, 96.7, 120.1, 121.9, 137.8, 143.5, 167.1, 208.1. Anal. Calcd. for $C_{13}H_{16}O_3$:C, 70.89; H, 7.32. Found: C, 70.69; H, 7.48. Characteristic ^{1}H NMR peaks of the (2*E*,4*Z*)-isomer were found at δ_H 2.16 (s, 3H), 2.49 (td, 2H), 2.64 (t, *J* 7.7, 2H), 5.75 (dt, *J* 10.4, 1H), 5.95 (d, *J* 15.7, 1H), 6.40 (t, *J* 11.1, 1H), 7.71 (dd, *J* 15.7, 11.3, 1H).

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